

Irradiation as an Alternative to Mastectomy for Early Breast Cancer

An Important Consideration Because of Changes in Laws

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Between May 1973 and December 1980 there were 76 patients (78 breasts) with clinical stage I or II breast carcinoma treated by biopsy and definitive radiotherapy at Stanford University Medical Center. Local-regional control has been achieved thus far in 76 of 78 cases (97 percent) with a median follow-up time of 26 months. Transient lymphedema of the breast, arm edema and breast fibrosis were the most commonly noted complications. The cosmetic result was analyzed and scored as excellent in 78 percent, satisfactory in 18 percent and unsatisfactory in 4 percent. The three unsatisfactory results occurred in patients in whom severe fibrosis developed as a result of suboptimal radiation techniques. Interdisciplinary cooperation among surgical, medical and radiation oncologists is important. The 97 percent local-regional control and the 96 percent excellent-to-satisfactory results support the use of primary radiotherapy in early stage breast carcinoma.

At the Division of Radiotherapy at Stanford University Medical Center we observed a significant change in the referral patterns of patients with cancer of the breast and we estimate that this change will be further accentuated in California by the passage in 1980 of a state bill mandating that physicians inform patients of alternative treatment methods in the management of breast cancer.* Similar legislation has been passed in Massachusetts and Minnesota.

In this paper we present a literature review of the results of primary radiotherapy in the treatment of early stage breast carcinoma and detail the Stanford University Medical Center experience with this form of treatment. Optimal care for patients with this disease requires close interaction and communication among surgical, medical and radiation oncologists. The inter-

disciplinary care of such patients will be emphasized, especially as it pertains to the radiotherapeutic management of this disease.

Review of Literature

While controversy continues regarding the use of primary radiation therapy in the management of breast carcinoma, this technique is not new. Considerable experience has been reported on from Europe where five- and ten-year results on large numbers of patients are available. In 1936 at the Fondation Curie, Francois Baclesse initiated a policy of "conservative management" that did not include mastectomy for patients who had operable breast cancer. This management has been pursued until the present, and in 1978 Calle and co-workers reported on the cases of 514 patients treated since 1960.² There was a minimum follow-up of five years and over half of the patients had been followed for at least ten years. In patients who had an excisional biopsy, a local control rate of 87 percent was achieved. Half of the local failures were free of disease five years following surgical salvage. Patients who had tumors greater than 3 cm had needle biopsy

*Under California law, physicians and surgeons may be disciplined for unprofessional conduct and the law specifies what constitutes such conduct. On September 17, 1980, California Senate Bill 1893 was signed by Governor Jerry Brown, adding section 1704.5 to the state's Health and Safety Code, effective January 1981. This bill adds to the definition of unprofessional conduct the following: "the failure of a physician and surgeon to inform a patient by means of a standardized written summary . . . of alternative efficacious methods of treatment which may be medically viable, including surgical, radiological or chemotherapeutic treatments or combinations thereof, when the patient is being treated for any form of breast cancer."¹

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ABBREVIATIONS USED IN TEXT

CMF=cyclophosphamide, methotrexate and 5-fluorouracil
 TNM=tumor-node-metastasis staging
 UICC=Union Internationale Contre le Cancer

only, and in this group local relapse was high, a fact that attests to the importance of excisional biopsy.

Spitalier and colleagues from the Cancer Institute in Marseilles reported on the cases of 400 consecutive patients treated between 1960 and 1970, with a minimum follow-up of five years.³ Treatment policy was similar to that at Fondation Curie, with excisional biopsy done only for tumors less than 3 cm. Local control was 92 percent in this group. Similarly, local control was a problem in patients who had large tumors and in whom only needle biopsy was done.

Recently Pierquin and associates⁴ published the five-year results on a series of 177 patients in which they achieved local control in 93 percent of stages I and II patients. Five- and ten-year survival rates reported in this French series are comparable to results obtained in large surgical series from Memorial Sloan-Kettering (New York)⁵ and Columbia Presbyterian (New York),⁶ for similarly staged patients.

Peters⁷ from the Princess Margaret Hospital in Toronto analyzed 217 cases of early stage breast cancer treated between 1939 and 1979 with excision and irradiation. These patients were compared with a control group treated by mastectomy and postoperative radiotherapy. The two groups were matched by age, tumor size and duration of follow-up. Local control was 93 percent in both groups. Overall survival and disease-free survival up to 30 years were not significantly different for the two groups.

Encouraged by the long-term results obtained by irradiation in Europe and Canada, Prosnitz and co-workers⁸ reviewed the combined experience of four major medical centers in the United States. Local control was 93 percent in 150 stages I and II patients treated between 1962 and 1975. Since this review, there has been a rapidly growing experience at many institutions in the US. In 1979 Montague and associates⁹ reported on the cases of stages I and II patients treated at MD Anderson Hospital (Houston) between 1955 and 1975. Local-regional control was 96 percent.

Hellman and colleagues¹⁰ recently updated the experience at the Joint Center for Radiation Therapy of the Harvard Medical School (Boston) with 184 cases of stages I and II breast carcinoma. With a median follow-up of 33 months, local-regional control was 95 percent and 93 percent for stages I and II. Other medical centers in the US have reported similar results.¹¹⁻¹⁶

Because of the long natural history of breast cancer, the US experience remains preliminary; but our two- and five-year results are in keeping with the excellent long-term results for patients treated by excisional biopsy and radiation therapy in the French series. Ad-

ditionally, survival remains comparable to similarly staged patients treated with radical surgical procedure.

The Cancer Institute in Milan has recently reported the findings of a randomized trial comparing the Halsted radical mastectomy with quadrantectomy, axillary dissection and postoperative radiotherapy to the remaining breast.¹⁷ There were 701 patients randomly selected between 1973 and 1980. Only patients who had clinical stage T₁N₀M₀ (tumor less than 2 cm, nodes 0, metastasis 0)* were entered. There were three local recurrences in the Halsted group and one in the quadrantectomy-radiation group. There were no differences in disease-free survival or overall survival. The authors concluded that "mastectomy appears to involve unnecessary mutilation in patients with breast cancer of less than 2 cm and no palpable axillary nodes."¹⁷

The National Cancer Institute has recently initiated a randomized trial to compare results of radical mastectomy with excisional biopsy and radiation. The National Surgical Adjuvant Breast Project is also conducting a randomized trial between modified radical mastectomy and segmental mastectomy, with or without postoperative radiotherapy. When the results become available, many of the questions concerning the local-regional management of early stage breast carcinoma should be answered.

During the 1970s multiple refinements in radiotherapy technique were made that improve not only local control but also the cosmetic result.^{18,19} The importance of an excisional biopsy to achieve maximal local-regional control and to reduce radiation dose has been well established in both the French series and in the Harvard experience.^{2,3,19} Obtaining the best cosmetic result is particularly important for a patient who finds the psychosocial impact of radical procedure unacceptable. Because breast preservation is the major advantage of primary radiotherapy, it is important to minimize posttreatment sequelae and concurrently obtain the best cosmetic result.

Because of increased public awareness concerning controversies in medical management of various diseases, particularly breast cancer, we have recently observed an increase in referrals to Stanford as patients search for treatment alternatives. We expect this trend to continue, especially in view of the recent California legislation. The current Stanford experience involving the radiotherapeutic management of breast cancer following excisional biopsy will be detailed.

Material and Methods

Patient Population

Between May 1973 and December 1980, 76 patients (78 breasts) with clinical stage I or II adenocarcinoma of the breast were treated by definitive radiotherapy at Stanford University Medical Center. All patients were

*Based on TNM staging of tumors established by the Union Internationale Contre le Cancer and the American Joint Committee for Cancer Staging and End Results Reporting (UICC/AJC).

clinically staged according to current UICC-TNM criteria.²⁰

Surgical Techniques

All patients were advised to have an excisional biopsy; this was carried out in 75 of 78 lesions. Two patients had incisional biopsy and one had a needle biopsy only.

Axillary dissection was recommended to patients who were candidates for adjuvant chemotherapy and this was done in 38 patients; 11 patients had axillary samplings and 29 did not have axillary staging.

Radiation Treatment Policy

Radiation treatment techniques have been discussed previously.^{11,12} Most patients received 4,500 to 5,000 rads to the breast and regional nodes. This was fol-

lowed by iridium 192 (¹⁹²Ir) implantation to the tumor bed in 64 cases; 8 patients had electron boosts to the tumor volume, 4 had linear-accelerator boost and 2 had no additional treatment.

Follow-up and Evaluation

At each follow-up visit, in addition to routine clinical examination, multiple treatment complications were evaluated and scored as mild, moderate or severe. Breast edema, breast fibrosis, arm edema and mobility, skin discoloration and sequelae from the excisional biopsy were systematically evaluated. Breast size (A, B, C or D) was determined, with A, B and C approximating the breast cup size and D for patients who wear D cup or greater. A cosmetic result of excellent, satisfactory or unsatisfactory was given. Currently patients are being interviewed for their own evaluation of cosmesis.

Results

Treatment Results

There were 32 cases of clinical stage I and 46 cases of clinical stage II carcinoma. In all, 44 patients were premenopausal and 34 postmenopausal (Table 1). Most patients requested referral to Stanford after refusing a mastectomy or were seeking a second opinion because of grave concerns regarding the loss of a breast. For these reasons our patients tended to be younger, with most being premenopausal (mean age, 49 years; range, 26 to 79 years).

The possibility of selection bias must always be considered in nonrandomized trials. All patients who had stages I and II cancer were considered radiation therapy candidates unless multiple masses were present in more than one breast quadrant or unless mammography showed malignant calcifications in more than one breast quadrant. There was a slight majority of T₁ tumors (Table 2); 15 of the 37 T₂ lesions were greater than 4.0 cm in size.

There have been two local-regional failures in a median follow-up time of 26 months (Figure 1). Both patients have undergone surgical salvage. One patient completed a course of cyclophosphamide, methotrexate and 5-fluorouracil (CMF) and the second patient is currently receiving CMF. They remain free of disease 10 and 15 months post relapse. Seven patients have had a systemic relapse (one stage I and six stage II). The actuarial relapse-free survival at four years is 75 percent. Six patients are alive but have disease, one patient died of disease and one patient died of a myocardial infarction 3½ years after completion of therapy. An autopsy showed no evidence of local or systemic disease.

Axillary Staging

Axillary staging was done in 38/44 (86 percent) of premenopausal patients, but only 11/34 (32 percent) of postmenopausal patients. Based on clinical-pathological findings, adjuvant chemotherapy was recommended for 12 patients and was initiated in 11 (one

TABLE 1.—Stanford University Hospital Clinical Stages I and II Breast Cancer, May 1973 to December 1980

Classification of Patients	Number	Tumor Stages	
		I Number	II Number
Premenopausal	44	20	24
Postmenopausal	34	12	22
TOTAL	78	32	46

TABLE 2.—Correlation of T (Tumor) Stage With N (Node) Stage*

N Stage	T Stage		Total
	T ₁ †	T ₂ ‡	
N ₀	32	30	62
N ₁	9	7	16
TOTAL	41	37	78

*Staging of tumors established by the Union Internationale Contre le Cancer and the American Joint Committee for Cancer Staging and End Results Reporting (UICC/AJC).

†T₁ = tumor size less than 2 cm.

‡T₂ = tumor size more than 2 cm and less than 5 cm.

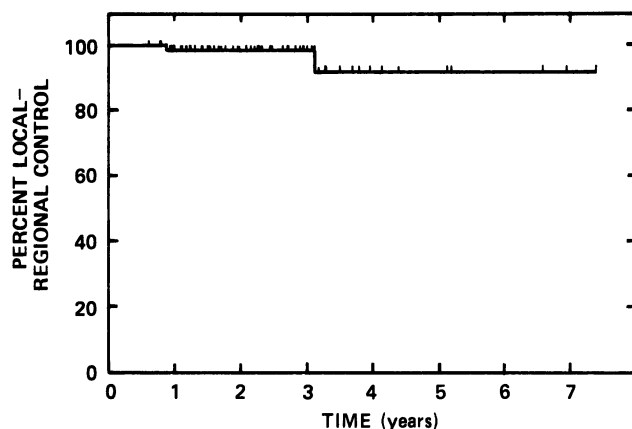


Figure 1.—Probability for local-regional control in 78 patients who have clinical stages I and II breast cancer treated by excisional biopsy and primary radiotherapy to the breast and lymph-node draining areas.

refused). In all, 62 patients had a clinically negative axilla; 37 underwent axillary staging and 7 were pathologically positive, for a false-negative rate of 19 percent (7/37). Of 16 patients who had a clinically positive axilla, 12 underwent axillary staging and 4 were pathologically negative, for a false-positive rate of 33 percent (4/12). Of the four patients who had pathologically negative axillary findings, however, only two had axillary dissections; the other two patients had lower axillary lymph node biopsy only. One of the patients who had a clinically positive axilla and negative results on lower axillary lymph node biopsy subsequently had relapse in the axilla and the tail of the breast simultaneously. The other patient had a persistently positive axillary node after a low axillary biopsy. She received high-dose axillary irradiation and is free of disease.

Cosmetic Results and Complications

Analyses of cosmetic results and complications have been discussed in detail.²¹ Transient lymphedema of the breast was observed following axillary dissection in 33 of 38 patients (87 percent), and actuarial analysis showed gradual improvement and resolution in two to three years. Arm edema was observed in ten patients after axillary dissection, for an incidence of 26 percent in the dissected population. Breast fibrosis was observed in 18 patients; 13 were scored mild, 2 moderate and 3 severe. The severe cases were seen following suboptimal radiation technique (high dose per fraction) used in patients treated early in the series. Transient hyperpigmentation of the skin was observed in most patients.

Uncommon complications included upper extremity thrombophlebitis in five patients, four of which immediately followed the axillary dissection. Painful post-irradiation myositis occurred in four patients. Mild radiation pneumonitis occurred in two patients, neither of whom required admission to hospital or steroid therapy. Axillary abscesses were seen in three patients, all of whom had axillary dissections.

The cosmetic result was evaluated and scored as excellent in 61 patients (78 percent), satisfactory in 14 patients (18 percent) and unsatisfactory in 3 patients (4 percent). The three poor results occurred in those in whom severe breast fibrosis developed. Eleven patients had compromised cosmesis due to a poorly planned incision at the time of excisional biopsy. This generally resulted from a vertical incision that did not run parallel to skin lines and resulted in subsequent breast retraction. Occasionally a biopsy was excessive or a single long incision was used for both the excisional biopsy and the axillary staging procedure.

There was a good correlation between the cosmetic result and the breast size. All patients with an A size had an excellent result, whereas only half of D-sized breasts were scored as excellent. However, 80 percent of patients with D breasts treated with 180 rads per fraction had an excellent result.

Discussion

Whereas breast carcinoma remains the most common cancer among women, and despite the fact that there are many large published series with varying treatments from which to draw conclusions, there continues to be heated controversy concerning the optimal management of this disease. Breast carcinoma seemingly represents a spectrum of diseases, ranging from a very aggressive, poorly responsive malignancy to a cancer with a long natural history that is responsive to multiple therapies. The many prognostic variables that have been identified, the multiple efficacious treatment modalities—both local and systemic—and the psychosocial ramifications of treatment all add to the complexity of devising a treatment plan for any one patient. This confusion has resulted in a California law that mandates that physicians are required to inform patients of “alternative efficacious methods of treatment which may be medically viable.”

Both local-regional and systemic management must be considered when planning therapy. Surgical procedure, radiation therapy or combinations thereof form the basis of local therapy. Radical mastectomy has proved effective as a local treatment in early stage breast cancer,^{5,6} but is associated with unacceptable morbidity for many patients, that is, loss of a breast. Because radiation therapy has been effective against other epithelial tumors, such as cancer of the cervix, prostate, and head and neck, and is beneficial in reducing local recurrence in high-risk breast cancer patients following radical surgical intervention, it should be effective in treating primary breast cancer following excisional biopsy. The large European series and evolving US experience support this contention.

The importance of removing the gross tumor by excisional biopsy for maximum local control has been well established.^{2,3,19} Because the major advantage of primary radiotherapy is breast preservation, however, efforts to keep treatment sequelae to a minimum and to obtain the best cosmetic result should be made. A well-planned incision with careful attention to Langer's lines or the use of a circumareolar incision when applicable will minimize later breast retraction and deformity.²² About 14 percent of patients in this series had a reduction in cosmesis as a result of the excisional biopsy.

In planning radiation therapy, knowledge of the precise location of the original tumor is important; that is, whether it was directly beneath the scar or somewhat adjacent, and whether the lesion was superficial or deep. This is particularly important with respect to type, location and dose of boost therapy to the tumor bed. For example, electron beam therapy to the nipple and areola frequently produces pain and discomfort and therefore centrally located lesions are best supplemented with ¹⁹²Ir implantation. On the other hand, in a patient with very small breasts whose tumor is located very medially on the chest wall or is overlying the pectoralis muscle, there may be insufficient breast tissue for op-

timal implantation. We have observed painful myositis in four patients in whom ^{192}Ir implants were placed in close proximity to, or inserted superficially into, the pectoralis muscles. In these patients booster therapy is best given with electrons.

The potential for early systemic spread of breast cancer is now increasingly appreciated. Adjuvant chemotherapy for breast cancer is dynamic and is evolving rapidly with increasing focus on both the timing and dose of drug administration. Patients who are candidates for adjuvant chemotherapy and for whom primary radiation is planned should have an axillary staging procedure because the state of the axillary nodes remains our best indicator of systemic disease. Either an axillary dissection or a thorough axillary sampling that resects all the nodes beneath the pectoralis muscle and inferiorly should be done. The importance of the axillary staging procedure is well known. Most series show that in 25 percent to 40 percent of patients with clinically negative axillae there will be positive nodes on axillary dissection (19 percent in this series). Additionally, some patients with clinically positive axillae may have negative dissections and can be spared full-course adjuvant chemotherapy. Of the 12 patients who were advised to have adjuvant chemotherapy in this series, 7 had a clinically negative axilla that proved to be pathologically positive, illustrating the importance of axillary dissection. Additionally, two patients who had clinically positive axillae had axillary dissections that gave negative results and thus they were advised not to receive chemotherapy. However, an additional two patients who had clinically positive axillae only had low axillary lymph node biopsy, results of which were pathologically negative, and in retrospect these two patients probably had axillary disease. We would therefore recommend a complete axillary dissection or a thorough axillary sampling in patients with clinically positive axillae in whom pathologic confirmation of disease cannot be made by frozen section at the time of axillary lymph node biopsy.

Multiple complications were associated with the axillary dissection, including lymphedema of the breast (89 percent), arm edema (26 percent), upper extremity thrombophlebitis (11 percent) and axillary abscess (8 percent). These were for the most part transient and self-limiting, however, and did not ultimately affect cosmesis.

Radiation technique was also extremely important. The most severe complications in this series, three cases of severe fibrosis, resulted from suboptimal radiotherapy technique. Thus, careful attention to the external beam therapy and appropriate selection of the type of boost therapy (^{192}Ir or electrons) are important. In conclusion, the importance of interdisciplinary cooperation in the management of patients who have early stage breast carcinoma cannot be overemphasized. Careful planning

of the excisional biopsy and axillary staging, followed by careful radiotherapy technique and the appropriate timing of adjuvant chemotherapy in selected patients, are all important components of diagnosis and treatment. Primary radiation therapy has been conclusively shown to be an effective alternative to radical mastectomy in patients with T_1 lesions (with or without positive axillary nodes at dissection).¹⁷ We must await the results of the National Cancer Institute trial and the National Surgical Adjuvant Breast Project (NSABP) cooperative trial, however, for confirmation of the efficacy of radiotherapy for larger lesions. Nonetheless, the 97 percent local-regional control and the 96 percent excellent-to-satisfactory cosmetic results achieved at Stanford support the use of primary radiotherapy as an alternative to mastectomy in the management of patients with stages I and II breast carcinoma.

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